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## CURRENT CONCEPTS IN CANCER

### Solid Tumors in Children

HAROLD M. MAURER, M.D.

**D**URING the past two decades substantial progress has been made in the treatment of pediatric solid tumors. Improved survival is accounted for by a better understanding of the natural history of the various tumors, improved histologic classifications, new technics to define extent of disease accurately, effective chemotherapy and improved radiation, surgical and supportive therapies. The purpose of this report is to review some of the common childhood tumors, emphasizing current management and investigations.

#### WILMS' TUMOR

Wilms' tumor is the most common intra-abdominal tumor of childhood. The median age at diagnosis is approximately 3½ years. Approximately 95 per cent of the tumors are unilateral, and, as in other pediatric tumors, there is a slight male preponderance.

The benefit of nephrectomy and postoperative radiotherapy to the renal bed was evident by the early 1960's. The two-year survival rate for children with resectable tumors without distant metastases ranged between 22 and 62 per cent, with younger patients having a better prognosis. In the meantime, Wilms' tumor was found to respond to dactinomycin, the first effective chemotherapeutic agent against a pediatric solid tumor. By the late 1960's, dactinomycin had a major place in treatment.

In a controlled study reported in 1968, Wolff demonstrated the benefit of multiple courses of dactinomycin given over 15 months in preventing metastases after nephrectomy and postoperative radiotherapy to the renal bed.<sup>1</sup> In the large co-operative National Wilms' Tumor Study treatment was further refined.<sup>2</sup> Postoperative irradiation of the renal bed was found to be unnecessary in children whose tumors were contained within the kidney (Group I). Unirradiated patients fared as well (>90 per cent two-year survival) with multiple courses of dactinomycin over 15 months as those receiving both postoperative radiation and dactinomycin. Combined dactinomycin and vincristine gave better survival results at two years (86 per cent) than either agent alone (67 to 72 per cent) in patients with more advanced disease (Groups II and III) still confined to the abdomen, all of whom received postoperative irradiation. Preliminary results of a subsequent investigation, the second National Wilms' Tumor Study, suggest that fewer dactinomycin and vincristine courses may be given to Group I

patients without jeopardizing the excellent survival rate, and that the addition of adriamycin (doxorubicin) increases survival in Groups II and III patients. Analysis of the tumor histopathology data from the Study revealed that it is possible to identify patients likely to do poorly when current therapeutic approaches are used, on the basis of cytologic atypism (anaplasia) or sarcomatous stroma in the tumor.<sup>3</sup> Studies are being designed to refine treatment for patients with favorable (well differentiated) histology and to intensify treatment for those with unfavorable histology.

#### NEUROBLASTOMA

The survival rate in neuroblastoma, a malignant tumor arising in the sympathetic nervous system, has improved little in the past 20 years in spite of advances in treatment of other tumors. This lack of substantial improvement is related to the facts that approximately 70 per cent of the patients have widespread disease at the time of diagnosis and that the effects of chemotherapy are variable and transient. Curiously enough, neuroblastoma is found in situ in the adrenal glands of one in 200 newborn infants and may undergo spontaneous regression or transformation to a benign ganglioneuroma.

Neuroblastoma occurs most frequently in the younger pediatric age group, with a median incidence in the child two years of age. Approximately 60 per cent of tumors arise in the abdomen. Seventy-five per cent of patients excrete increased amounts of catecholamine metabolites in the urine, a useful indicator of tumor activity.

The prognosis in neuroblastoma is influenced mainly by age, stage and primary-tumor site. In children less than one year of age the two-year relapse-free survival rate is 75 per cent, and over the age of two, it is 12 per cent. Survival rates for Stages I, II and IV-s range from 63 to 85 per cent, whereas for Stages III and IV, they are 37 per cent and 5 per cent respectively.<sup>4</sup> Thoracic lesions are more favorable than abdominal tumors.

Operation alone may be curative when the tumor is localized and completely excised. The role of radiation therapy is not well defined although it is commonly used after incomplete resection or for control of metastases. The paucity of chemotherapeutic agents with predictable uniform cytotoxic effects on this tumor and the early development of drug resistance are the major problems in treatment. Cyclophosphamide and doxorubicin are the most effective agents and individually induce regression of tumors in 10 to 80 per cent of patients. Vincristine is less active, and the responses are variable and of short duration. The combination of the two or three agents induces tumor regression in 50 per cent of patients, but the duration of response is generally less than a year.<sup>5</sup> Immunotherapy has also been disappointing. Other agents of uncertain usefulness are imidazole carboxamide, papaverine, cis-platinum and the epipodophylotoxin,

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VM-26. Total-body irradiation is another approach of uncertain value.

Cell kinetic data indicate that the proliferating fraction of the tumor-cell population in neuroblastoma is small.<sup>6</sup> A large nonproliferating pool of cells may represent a major limitation to eradication of the tumor by chemotherapeutic agents.

#### RHABDOMYOSARCOMA

This tumor, the most common soft-tissue sarcoma found in childhood, can arise virtually anywhere in the body. The most frequent sites of origin in order of frequency are the head-and-neck region, extremities, genitourinary tract and trunk. Approximately 70 per cent of cases present before the age of 10.

There are four histologic subtypes of rhabdomyosarcoma, the most common form being embryonal followed by alveolar, botryoid and pleomorphic. Recently, a new variant occurring in soft tissue but considered histologically indistinguishable from Ewing's sarcoma of bone has been described and is referred to as "extraskelatal Ewing's tumor."<sup>7</sup> This subtype is as responsive to therapy as the classic forms.

The multidisciplinary Intergroup Rhabdomyosarcoma Study, concluded in 1978, has shed considerable light on the clinical characteristics of rhabdomyosarcoma and on specific problems in therapy.<sup>8</sup> The Study's clinical staging classification for the tumor has proved to be of major prognostic value and an aid in treatment planning. It is evident from the Study's data that lymphatic metastases occur in at least 18 per cent of patients presenting with genitourinary and extremity primary sites. Paratesticular primary tumors are associated with para-aortic-lymph-node involvement in 40 per cent of cases, indicating a need for lymph-node biopsy in these patients. Direct meningeal extension of tumor occurs within one year in 35 per cent of patients whose primary sites are in the head and neck (nasopharynx-nasal cavity, paranasal sinuses or middle ear) adjacent to the meninges. Extremity primary tumors also tend to metastasize to the central nervous system with increased frequency.

Additional results indicate that postoperative irradiation of the tumor bed is unnecessary when vincristine, dactinomycin and cyclophosphamide are given in combination for two years after excision of a localized tumor (Group I). Interestingly enough, this combination is no better than that of vincristine and dactinomycin in patients with microscopic residual disease (Group II), who receive postoperative irradiation as well. Intensive chemotherapy regimens, "pulse" vincristine, dactinomycin and cyclophosphamide alone or combined with doxorubicin, followed by irradiation, are equally effective in advanced stages and cause tumor regression in 80 per cent of patients having gross residual disease after operation (Group III) or metastatic disease at diagnosis (Group IV). At present, the two-year relapse-free survival rates are projected to be 85 per cent for Group I, 72 per cent for Group II, 60 per cent for Group III and 25 per cent for

Group IV disease, with the overall survival rates being higher for each group.

Current investigations include a primary chemotherapy approach to avoid the disability associated with the various forms of exenteration for selected favorable sites — e.g., genitourinary tract "prophylactic" central-nervous-system irradiation for patients with head-and-neck parameningeal primary tumors, reduction in radiation doses and more intensive chemotherapy for patients with advanced disease.

#### HODGKIN'S DISEASE

Hodgkin's disease is the most common lymphoma in childhood. Patterns of disease are similar in adults and children although the tumor is rare in children under five years of age. Treatment decisions and prognosis depend on histologic type and stage of disease determined clinically, radiographically and surgically. Laparotomy with splenectomy alters the clinical stage in one third of the cases. Nodular sclerosis is the most common histologic subgroup, followed in frequency by mixed cellularity, lymphocytic predominance and lymphocytic depletion — the last rarely encountered in children.

Irradiation is the cornerstone of treatment for Stages I and II and is delivered to a "mantle field" and to the para-aortic nodes and splenic pedicle or to involved fields only.<sup>9</sup> Total nodal irradiation offers the least chance of relapse by disease extension into unirradiated nodes. Involved-field irradiation supplemented with chemotherapy may offer the same advantage and avoid the potential deleterious late effects of irradiation on the growing child. A comparative intergroup trial of these two technics is now being conducted. The five-year survival rate in Stages I and II is 90 per cent, with further moderate attrition between five and 10 years.

In patients with more advanced disease (Stages III and IV), the benefits of chemotherapy have been clearly demonstrated. Approximately 70 to 80 per cent of patients achieve a complete response with six months of nitrogen mustard, vincristine, prednisone and procarbazine treatment, but half the patients relapse during the first three to four years of follow-up observation.<sup>10</sup> The development of resistance to this set of drugs does not necessarily imply resistance to others. Other effective drugs include cyclophosphamide, vinblastine, doxorubicin, bleomycin, imidazole carboximide, lomustine and VM-26. The evidence at present suggests that, for the more advanced stages, extended-field irradiation combined with chemotherapy produces the lowest relapse rate, although the exact role of the two is incompletely defined.

#### NON-HODGKIN LYMPHOMA

Non-Hodgkin lymphomas arise from nodal, extranodal or nonlymphatic sites, tend to disseminate early and progress rapidly. The disease occurs most commonly between the age of two and 12 years. The

Rapaport histologic classification developed for adults is of uncertain value when applied to children, since most childhood cases are not of the nodular histologic type. The classification of tumor cells by immunologic markers may provide an additional approach to classification and, ultimately, treatment planning. Whether staging laparotomy is of value in treatment or prognosis is not clear as yet. In children with tumors originating in the mediastinum or lymph nodes leukemic transformation and meningeal disease frequently develop.

When the disease is confined to the gut and regional mesenteric nodes, segmental resection plus postoperative whole-abdomen irradiation is curative in 80 per cent of patients.<sup>11</sup> For disease elsewhere, the current approach combines irradiation and multiple-agent intensive chemotherapy. The most successful therapeutic regimen reported to date combines intensive induction and consolidation chemotherapy with radiation, prophylactic central-nervous-system and cyclic maintenance therapies.<sup>12</sup> Cyclophosphamide, prednisone, vincristine, daunorubicin, cytarabine hydrochloride (cytosine arabinoside), L-asparaginase, carmustine, thioguanine, hydroxyurea and methotrexate are employed together in a tolerable schedule. Of 43 children treated with this protocol, 76 per cent are surviving relapse free with a median observation time of 25+ months. Fifty-one per cent of the survivors are off therapy, without evidence of disease. These preliminary results show promise, but require confirmation in a larger series of patients.

### OSTEOSARCOMA

Osteosarcoma, a malignant bone tumor, may arise in any bone, but is most common in the metaphyseal portion of long bones, especially the distal femur. Eighty per cent of all cases occur during the second decade of life. Until recently, chemotherapy trials were disappointing, and radical surgery alone or irradiation of the tumor followed by radical surgery had yielded a long-term survival rate of less than 20 per cent. Two notable advances in treatment include aggressive surgery for lung metastases<sup>13</sup> and adjuvant therapy with either doxorubicin<sup>14</sup> or high-dose methotrexate with citrovorum "rescue."<sup>15</sup> The combination of aggressive surgery to pulmonary metastases and adjuvant chemotherapy after resection of the primary tumor has increased the relapse-free survival at 18 months to over 55 per cent. Multidrug regimens acronymically designated CONPADRI-I (cyclophosphamide, vincristine, doxorubicin and phenylalanine mustard) and CONPADRI-II,III (includes high-dose methotrexate) have given comparable survival rates.<sup>16</sup> The strategic administration of drugs has permitted innovative surgical approaches such as en bloc resection of tumors and preservation of limbs by means of prosthetic devices in carefully selected patients.<sup>17</sup> In this regard, angiography has been extremely useful in demonstrating tumor boundaries. Other therapeutic approaches under investigation in-

clude adoptive immunotherapy, transfer factor and interferon, but none of these measures have been as effective as chemotherapy. With improved survival, the importance of early initiation of rehabilitation is crucial.

### EWING'S SARCOMA

Ewing's sarcoma is thought to originate from immature reticulum cells or primitive mesenchyme of the medullary cavity, but its exact histogenesis remains an enigma. As in osteosarcoma, the peak incidence is in the second decade of life. It arises most commonly in the bones of the trunk, or in the midshaft or metaphyseal portions of the long bones, especially the femur.

The previously dismal outlook in this tumor has improved considerably, and an actuarial five-year relapse-free survival rate of 75 per cent is reported for patients with localized disease.<sup>18</sup> The approach to treatment has evolved from one of primary surgery or primary radiation therapy to a combination of surgery, radiation and multidrug chemotherapy. The Intergroup Ewing's Sarcoma Study has shown that the addition of either doxorubicin or bilateral pulmonary irradiation to chemotherapy with vincristine, dactinomycin and cyclophosphamide and local irradiation improves the response and survival of children with nonmetastatic disease.<sup>19</sup> The intensive Memorial Hospital T-6 regimen, which in addition includes bleomycin, carmustine and methotrexate, also shows promise.<sup>18</sup> Relapse rates remain disturbingly high in patients with pelvic and sacral primary tumors regardless of the regimen employed. Failure is more often due to distant metastases than to relapse at the primary site. Because local and distant failure rates are lower when partial or complete resection is performed, and because of the functional disability seen with high-dose irradiation, surgical resection of the lesions in expendable bones is currently being explored.

Of great concern has been the failure to prevent re-appearance of disease and effect prolonged survival in patients presenting with metastatic disease. The discovery of new agents may be required to improve the survival in this group.

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## LAW-MEDICINE NOTES

### Confidentiality of Records in PSRO'S

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ONE of the most important experiments in medical-care regulation of this country in the 1970's is the group of organizations called PSRO's, or Professional Standards Review Organizations. These organizations were designed by the United States Congress to allow the medical profession the opportunity to monitor the quality and appropriateness of the medical care rendered to hospital patients covered by federally financed health care, mainly Medicare and Medicaid.

PSRO's are organized all across the country as nonprofit, private corporations. They generally view themselves as nongovernmental. The Department of Health, Education, and Welfare seems to agree with this view. However, it is clear that the Department exercises very tight control of PSRO structure, policy and operations by its contracts with each PSRO and by its detailed statutes and regulations in the field.

Nearly all PSRO executives and most physicians in this country believe that confidentiality of data, particularly of personal data on patients and providers, is essential to the success of the program. Probably the

most sensitive data in the eyes of physicians are the *PSRO physician profiles*, which might be sought by public-interest groups to provide to consumers in choosing a physician, by a malpractice attorney seeking support for a negligence claim or by a medical licensing board seeking evidence of a pattern of practitioner incompetence.<sup>1</sup>

A public-interest group in the District of Columbia called Public Citizen Health Research Group brought an action in the Federal Court to open up the records of the District of Columbia PSRO to public examination under the Federal Freedom of Information Act. The action caused great concern among PSRO's all over the country. The American Association of PSRO's joined in the action as an intervening party defendant, thus making it a national test case for the applicability of the Freedom of Information Act to this regulatory program. The District Court heard the arguments and ruled that the Act was applicable and issued an order to the PSRO and the Department to process the request for information.<sup>2</sup>

The controlling issue in the case was whether regional PSRO's are private organizations, as the PSRO's maintained, or federal agencies, as the plaintiff maintained. The PSRO cited a number of aspects indicating their private character, including the facts that the relation of PSRO's to the federal government is contractual, that the PSRO's are not established by federal law, that the staffs of the PSRO's are not federal employees, and that supervision by the Department of Health, Education, and Welfare is by regulation (and contract) and not on a day-by-day basis as with agencies that are clearly part of the federal government.

Judge Gesell was not impressed with these arguments. He applied the definition of "Federal Agency" found in the Administrative Procedure Act and interpreted in court decisions.<sup>3</sup> Under these interpretations it was found that the government utilizes private and quasi-private agencies to accomplish government objectives and to get the business of government done. The most important consideration was found to be whether the entity in question had authority in law to make decisions. Contrary to the defendants' arguments, it was found that PSRO's make many decisions daily that are authoritative within the PSRO program. In addition, however, Judge Gesell found many other factors compelling in finding PSRO's clearly to be federal agencies. He concluded

NCMF (the regional PSRO) is financed by the United States, it is a creature of statute, it performs an executive function, and it operates under direct, pervasive, continuous regulatory control affecting even minutia of the procedures and functions.

This decision was directed to answering this "agency" question. It remains for a further determination to be made as to whether the exemptions in the Freedom of Information Act apply to prevent disclosure of some or all of the data sought by the plaintiffs. The decision itself is now on appeal, so that one cannot be sure